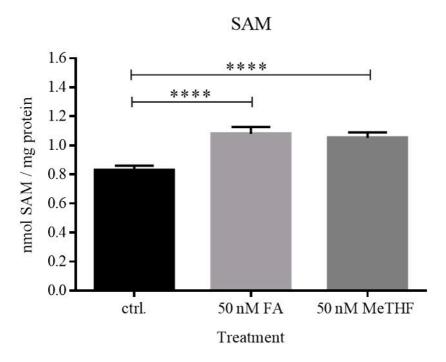
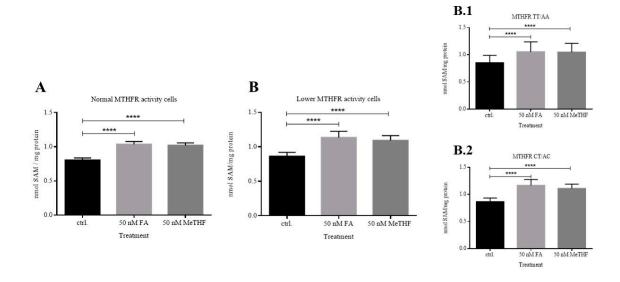


Supplementary Figure 1: Intracellular 5-Me-THF concentrations in (A) NORMAL MTHFR activity cells (genotype 677CC/1298AA, 677CT/1298AA, 677CC/1298AC, and 677CC/1298CC) (N=12) and in (B) LOW MTHFR activity cells (genotype 677TT/1298AA and 677CT/1298AC) (N=15). (B.1) LCLs with 677TT/1298AA genotype (N=5) and (B.2) LCLs with 677CT/1298AC genotype (N=10). Statistical differences were determined by one-way ANOVA with post-hoc Tukey's multiple comparisons test. Values are means \pm SD. * $p \le 0.05$, *** $p \le 0.01$, ***** $p \le 0.0001$, compared to untreated control (ctrl.).

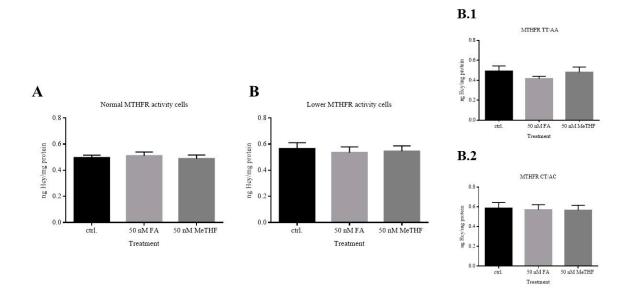


Intracellular concentration of SAM [ngmol SAM / mg protein]		AM
Ctrl. (mean ± SD)	50 nM FA (mean ± SD)	50 nM 5-Me-THF (mean ± SD)
0.829 ± 0.180	1.080 ± 0.263	1.052 ± 0.213

Supplementary Figure 2: Intracellular SAM concentration in folate-depleted cells (ctrl.) and after FA or 5-Me-THF treatment in LCLs. LCLs (N=35) were treated with equimolar concentration of folate supplements for 72h, then they were lysed and the concentration of SAM was measured with HPLC-UV/vis. Statistical differences were determined by one-way ANOVA with post-hoc Tukey's multiple comparisons test. Values are means \pm SD. **** p \leq 0.0001, compared to control.



Supplementary Figure 3: Intracellular SAM concentrations in (A) NORMAL MTHFR activity cells (genotype 677CC/1298AA, 677CT/1298AA, 677CC/1298AC, and 677CC/1298CC) (N=12) and in (B) LOW MTHFR activity cells (genotype 677TT/1298AA and 677CT/1298AC) (N=15). (B.1) LCLs with 677TT/1298AA genotype (N=5) and (B.2) LCLs with 677CT/1298AC genotype (N=10). Statistical differences were determined by one-way ANOVA with post-hoc Tukey's multiple comparisons test. Values are means \pm SD. **** $p \le 0.0001$, compared to untreated control (ctrl.).



Supplementary Figure 4: Intracellular Hcy concentrations in (A) NORMAL MTHFR activity cells (genotype 677CC/1298AA, 677CT/1298AA, 677CC/1298AC, and 677CC/1298CC) (N=12) and in (B) LOW MTHFR activity cells (genotype 677TT/1298AA and 677CT/1298AC) (N=15). (B.1) LCLs with 677TT/1298AA genotype (N=5) and (B.2) LCLs with 677CT/1298AC genotype (N=10). Statistical differences were determined by one-way ANOVA with post-hoc Tukey's multiple comparisons test. Values are means ± SD. There were no statistical significant changes on intracellular Hcy after the addition of folate supplements, compared to untreated control (ctrl.).

Supplementary Table 1: Genotype of the ten common polymorphisms of genes involved in folate uptake and metabolism in LCL cells.

Gene (polymorphism)

D
105) 93)
1112 GA
1112 GA CT CC AA TT AA AG GG CT CC 1122 GA CC CA GG CC AC AG GG TT CC 1515 GA CT CA GA CT AC AG GA TT TT 1516 GG TT CA AA TT AA GG GG CC CT 1570 AA CT CA GG CC AC AA GA CT TT 1754 AA CC CC GA CT AC AA GG CT CT 1880 / CC CC AA CC AA CT CC
1122 GA CC CA GG CC AC AG GG TT CC 1515 GA CT CA GA CT AC AG GA TT TT 1516 GG TT CA AA TT AA GG GG CC CT 1570 AA CT CA GG CC AC AA GA CT TT 1754 AA CC CC GA CT AA AG GG CT CT 1801 / CC CC AA CC AA <
1515 GA CT CA GA CT AC AG GA TT TT 1516 GG TT CA AA TT AA GG GG CC CT 1570 AA CT CA GG CC AC AA GA CT TT 1728 GA CC CC CA CT AC AA GA CT TT CC 1754 AA CC CC CA AC CT AA AG GG CT CT 1801 // CC CC AA CC AA AA AA AA AA AA AA AA CT CC CT CT AA AA AA AA CT CC CC CC CC CT AA AA AA AG GG CC CC CT CT AA AA
1516 GG TT CA AA TT AA GG GG CC CT 1570 AA CT CA GG CC AC AA GA CT TT 1728 GA CC CC CC GA CT AC AA GA TT CC 1754 AA CC CC AA CT AA AG GG CT CT 1801 / CC CC AA CC AA CC CT AA AG GG CC CC CC AA CT AA AG <t< th=""></t<>
1570 AA CT CA GG CC AC AA GA CT TT 1728 GA CC CC GA CT AC AA GA TT CC 1754 AA CC CC CC AA CT AA AG GG CT CT 1801 / CC CC AA CC AA AA AA AA CT CT 1823 GG CT CC GA CT AC AG GA CC CC 1976 GG CT CC GG CT AA AG GG CC CT 4995 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AG GG CC CT 5876 GG CT
1728 GA CC CC GA CT AC AA GA TT CC 1754 AA CC CC AA CT AA AG GG CT CT 1801 / CC CC CC AA CC AA AA AA CT CC 1823 GG CT CC CGA CT AC AG GA CC CC 1976 GG CT CC GG CT AC AG GG CC CT 4995 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AG GG CC CT 4995 AA CT CC GG CT AA AG GG CC CT 5876 GG CT CC
1754 AA CC CC AA CT AA AG GG CT CT 1801 / CC CC CC CC CC CA AA AA AA CT CC 1823 GG CT CC GA CT AC AG GA CC CC 1976 GG CT CC GG CT AC AG GG CC CT 4973 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AA AG GG CC CT 4995 AA CT CC GG CT AA AG GG CC CT 4995 AA CT CC GG CT AA AG GG CC CT CT AA AG
1801 / CC CC AA CC AA AA AA CT CC 1823 GG CT CC GA CT AC AG GA CC CC 1976 GG CT CC GG CT AC AG GG CC CT 4973 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AA AG GG CC CT 5876 GG CT CC AA CT AC AA AG GG CT TT 6037 GA CC CC AA CT AC AG GG TT TT 6127 GA CC CC CA GA CT AC AG GG CC CC 6153 GA
1823 GG CT CC GA CT AC AG GA CC CC 1976 GG CT CC GG CT AC AG GG CC CT 4973 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AA AG GG CC CT 5876 GG CT CC AA CT AC AA GG CT TT 6037 GA CC CC AA CT AC AG GG TT TT 6127 GA CC CA GA CT AC AG GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC
1976 GG CT CC GG CT AC AG GG CC CT 4973 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AA GG CC CT 5876 GG CT CC AA CT AC AA GG CT TT 6037 GA CC CC AA CT AA AG GG TT TT 6127 GA CC CA GA CT AC GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC CA AT TT AA AG GG CC CT 6203 GA CT CC
4973 AA CT CC GA CT AA AG GG CC CT 4995 AA CT CC GG CT AA AA GG CC CT 5876 GG CT CC AA CT AC AA GG CT TT 6037 GA CC CC AA CT AA AG GG TT TT 6127 GA CC CA GA CT AC GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GG CC CC 6159 GG CC CC AA CT AA AG GG CC CT 6203 GA CT CC AA
4995 AA CT CC GG CT AA AA GG CC CT 5876 GG CT CC AA CT AC AA GG CT TT 6037 GA CC CC AA CT AA AG GG TT TT 6127 GA CC CA GA CT AC GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GA CC CC 6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG
5876 GG CT CC AA CT AC AA GG CT TT 6037 GA CC CC AA CT AA AG GG TT TT 6127 GA CC CA GA CT AC AG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GG CC CT 6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CC CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA
6037 GA CC CC AA CT AA AG GG TT TT 6127 GA CC CA GA CT AC GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GA CC CC 6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AG GG CT TT 6425 AA CT AA GG
6127 GA CC CA GA CT AC GG GA CC CC 6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GG CC CT 6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AG GG CT CC 6425 AA CT AA GG GG CT TT 6429 GG CT CC GA CT AC GG
6153 GA CC CC GA CT AC AG GA CC CC 6159 GG CC CC AA TT AA AG GG CC CT 6203 GA CT CC AA CT AA AG GG CC CT 63333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AA AG GG CT CC 6423 AA CT AA AG AA AG AA AG GG CT CC 6425 AA CT AA AG GG GG CT TT 6429 GG CT CC GA
6159 GG CC CC AA TT AA AG GG CC CT 6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AG GG CT CC 6425 AA CT AA GA TT AA AG GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC
6203 GA CT CC AA CT AA AG GG CC CT 6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AA GG CT CC 6425 AA CT AA GA TT AA GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA CC AA AG GA CT TT TT TT TT TT TT TT
6333 GA CT CC AA CT AC AG GG CT CC 6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AA GG CT CC 6425 AA CT AA GA TT AA GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA CC CC 382 GA TT CC AA CT AA
6417 GA CT CC GG CT AA AG GG CC CC 6423 GG CC CA AA TT AA AA GG CT CC 6425 AA CT AA GA TT AA GG GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA TT TT 382 GA TT CC AA CT AA AG GA CC CC
6423 GG CC CA AA TT AA AA GG CT CC 6425 AA CT AA GA TT AA GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA TT TT 382 GA TT CC AA CT AA AG GA CC CC
6425 AA CT AA GA TT AA GG GG CT TT 6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA TT TT 382 GA TT CC AA CT AA AG GA CC CC
6429 GG CT CC GA CT AC GG GG CC TT 6430 GA TT CA GA CT AC GG GA CT CC 380 AA CC CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA TT TT 382 GA TT CC AA CT AA AG GA CC CC
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380 AA CC CC AA CC AA AG GG CT TT 381 AA CT CC GA CC AA AG GA TT TT 382 GA TT CC AA CT AA AG GA CC CC
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382 GA TT CC AA CT AA AG GA CC CC
202 GA TT GA AA GT AG GG GT GT
383 GA TT CA AA CT AC GG GG CT CT
384 GA CT CC AA CC AC AG GG CC TT
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390 GG CT CC AA CC AC GG GG CT CT